Note Added in Proof: The difficulties associated with epoxidation of *Z*-allylic alcohols in the present work are not avoided by utilizing only *E*-allylic alcohols. In this way one obtains the erythro diol relationship by DIBAL reduction of, for example, 18 to the corresponding erythro aldehyde. Whereas, treatment of 18 with K_2CO_3 in MeOH leads, via epimerization, to an almost quantitative yield of the corresponding threo aldehyde. The epimerization process is general, and we have used it in highly selective syntheses of all four pentoses and all eight hexoses.

Supplementary Material Available: A listing of spectral data (9 pages). Ordering information is given on any current masthead page.

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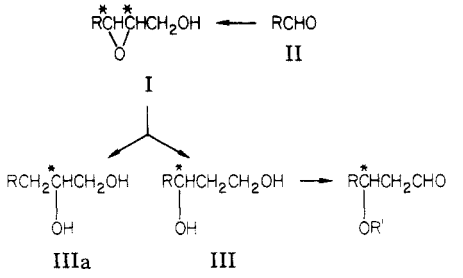
Synthesis of Saccharides and Related Polyhydroxylated Natural Products. 2. Simple Deoxyalditols

Summary: Asymmetric epoxidation of allylic alcohols followed by selective hydride reduction provides a new route to chiral 1,3-diols and 1,3,5-triols; one of the 1,3,5-triols (**21**) is also synthesized from D-glucose.

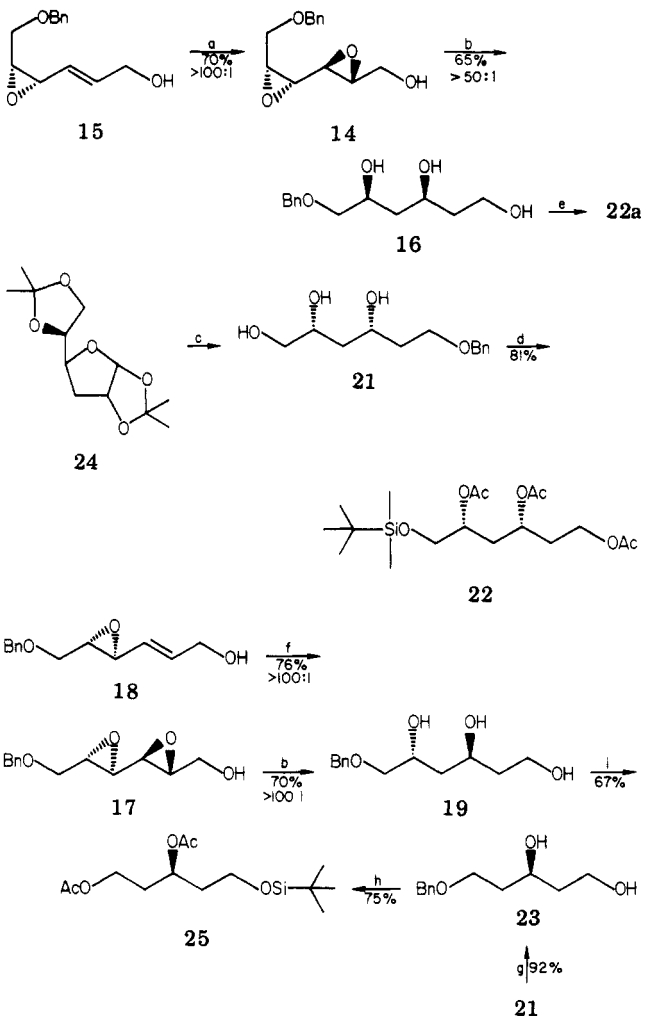
Sir: The preceding communication describes the selective synthesis of most, if not all, of the four possible stereoisomeric epoxy alcohols (I) from a variety of aldehydes RCHO (II).[1] Of many useful transformations that these versatile synthetic intermediates (I) may undergo, reductive ring opening attracts special attention. It (reduction) should provide two regioisomeric diols (III and IIIa), the ratio of which would change with three variables: the R group and stereochemistry of the epoxide in I and the reductant used in the reaction. We have found that the reduction of I, where the R group carries an ethereal substituent (or substituents) α and/or β to the epoxide, leads to the (nearly) exclusive formation of III with sodium bis(methoxyethoxy)aluminum hydride (Red-al) under normal conditions. This finding, although seemingly trivial, bears synthetic significance and indeed constitutes an essential step of sequence B, one of the two fundamental two-carbon extension sequences described earlier.[1]



(B)

(1) Katskuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J., preceding paper in this issue.

Scheme I



[a] (a) $Ti(OPr)_4$, (−)-DET, TBHP (CCl_4), −20 °C, 3 h. (b) Red-al (THF), 22 °C, 3 h. (c) i, 0.8% H_2SO_4 (MeOH), 22 °C, 15 h, 86%; ii, $(C_3H_3N_2)_2C(=S)$ (THF), reflux, 5 h; iii, $(Me_2O)_3P$, 110 °C, 10 h; iv, disiamylborane (THF), NaOH, H_2O_2, 50%; v, NaH, $PhCH_2Br$ (DMF), 50 °C, 5 h, 87%; vi, Dowex 50W-X8 resin (H_2O), 50 °C, 2 h, 100%; vii, $NaBH_4$ (EtOH), 22 °C, 2 h, 100%. (d) i, TBDMS-Cl, DMAP (CH_2Cl_2), 22 °C, 5 h; ii, H_2, 5% Pd/C (MeOH), 22 °C, 8 h; iii, Ac_2O, C_5H_5N, 60 °C, 5 h. (e) i, Ac_2O, C_5H_5N, 60 °C, 5 h; ii, H_2, 5% Pd/C (MeOH), 22 °C, 12 h; iii, TBDMS-Cl, DMAP (CH_2Cl_2), 22 °C, 5 h. (f) $Ti(OPr)_4$, (+)-DET, TBHP (CH_2Cl_2), −20 °C, 18 h. (g) i, $NaIO_4$ (H_2O), 22 °C; ii, $NaBH_4$ (EtOH), 27 °C, 10 h. (h) i, TBDMS-Cl, DMAP (CH_2Cl_2), 22 °C, 5 h; ii, H_2, 5% Pd/C (MeOH), 22 °C, 8 h; iii, Ac_2O, C_5H_5N, 60 °C, 5 h. (i) i, TBDMS-Cl, DMAP (CH_2Cl_2), 22 °C, 5 h; ii, H_2, 5% Pd/C (MeOH), 22 °C, 8 h; iii, $NaIO_4$ (H_2O), 22 °C; iv, $NaBH_4$ (EtOH), 22 °C, 10 h; v, Ac_2O, C_5H_5N, 60 °C, 5 h.

Table I summarizes preliminary results. While lithium aluminum hydride (reagent L) or Red-al (reagent R) reduction of **1** (where R in I is *n*-alkyl) yields the 1,2-diol (**2**) and 1,3-diol (**2a**) in nearly equal amounts, some regioselection is already evident in the reaction of **3** and **4** (entries 2, 3), favoring the formation of 1,3-diols (**5** and **6**). This trend culminates with the epoxy alcohols **7**–**10** (entries 4–7), which are oxygenated at the positions α or α and β to the epoxide, where the use of Red-al leads to the (almost) exclusive formation of the 1,3-diols **11**–**13**. The absolute configuration has been correlated with that of (*R*)-(+)-malic acid,[2] and compound **12** has been converted to its tetraacetate **12a**, identical with that derived from 2-deoxy-D-*erythro*-pentose via sodium borohydride re-

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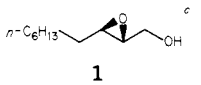
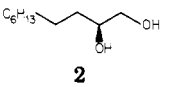
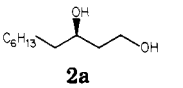
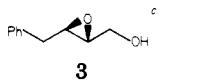
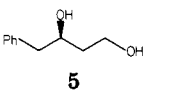
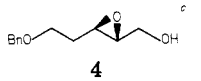
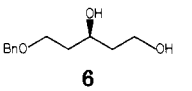
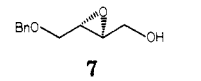
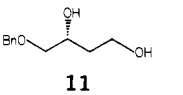
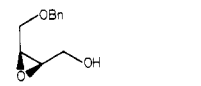
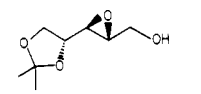
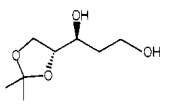
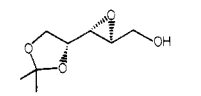
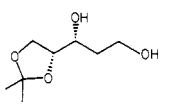
Table I. Reductive Opening of Epoxy Alcohols (I)

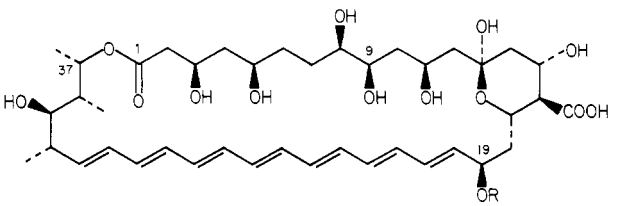
entry	epoxy alcohol	reductant[a] (rctn temp, °C)	III/IIIa[b]	% yield	structure of the major diol
1	 1	L (0)	1:1	94	 2
		R (0)	1:1	96	 2a
2	 3	L (0)	5:1	77	 5
		R (0)	5:1	92	
3	 4	L (0)	5:1	77	 6
		L (−20)	9:1	78	
		R (0)	5:1	89	
4	 7	L (0)	4:1	90	 11
		R (0)	40:1	98	
5	 8	L (0)	11:1	96	
		R (0)	100:1	95	11
6	 9	R (0)	>100:1	78	 12
7	 10	R (0)	>100:1	82	 13

[a] L and R denote lithium aluminum hydride and Red-al, respectively. [b] The ratios of III and IIIa were determined by ^1H NMR (250 or 270 MHz) spectroscopy and/or by HPLC analysis. The signals due to IIIa are readily identified as IIIa is oxidized with $NaIO_4$. [c] The racemates were used in these experiments.

duction and acetylation.[3] Compound Red-al is a 1,3-diol[4] and differs from **12**; therefore, it must have the stereochemistry shown in **13**.

The regioselectivity demonstrated above is not limited to the reduction of *monoepoxy* alcohols. Two dramatic examples follow (see Scheme I). Thus, the 2,3:4,5-diepoxy alcohol **14**,[5] prepared from the 4,5-epoxy allylic alcohol **15** via asymmetric epoxidation, undergoes clean double ring opening to provide a single product, 1,3,5-triol **16**. A ^1H NMR spectrum of the crude reduction mixture remains virtually unchanged upon exposure to sodium metaperiodate. Similarly, Red-al reduction of diepoxy alcohol **17** obtained from **18** provides **19** exclusively. The assignments of stereochemistry to these triols as shown in **16** and **19** are almost secure on the basis of mechanistic considerations but have been confirmed by correlation with the stereochemistry of D-glucose (vida infra).

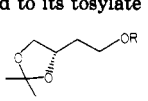
The above findings, in particular, the simultaneous creation of two hydroxylated chiral centers are important. The synthesis of many polyacetate natural products, as exemplified by amphotericin B (**20**),[6] requires construction



20

of the 1,3-diol system with high diastereo- and enantioselection, a problem that has challenged synthetic chemists in recent years. The use of an available monosaccharide

(2) The known alcohol i prepared from (*S*)-(−)-malic acid according to a known procedure (Mori, K.; Takigawa, T.; Matuo, T. *Tetrahedron*, **1979**, *35*, 933) was converted to its tosylate (ii).



i, R = H
ii, R = Ts

This compound ii was found to be identical, except for signs of rotation, with that obtained from **11** through a sequence of reactions: (i) hydrogenolysis, (ii) acetonide formation, and (iii) tosylation. See also Clercq, P. D.; Mijngheer, R. *Bull. Soc. Chim. Belg.* **1978**, *87*, 495.

(3) Abdel-Akher, M.; Hamilton, J. K.; Smith, F. *J. Am. Chem. Soc.* **1951**, *73*, 4691.

(4) Compound **13** is inert to sodium metaperiodate oxidation.

(5) Compound **14** is very sensitive to acid, and proper precautions must be taken in its handling.

(6) (a) Isolation from *Streptomycetes nodosus*: Vandeputte, J.; Wachtel, J. L.; Stiller, E. T. *Antibiot. Ann.* **1956**, 587. (b) Chemical degradation: Borowski, E.; Mechlinkski, W.; Falkowski, L.; Ziminski, T.; Dutcher, J. D. *Tetrahedron Lett.*, **1965**, 473. Cope, A. C.; Axen, U.; Burrows, E. P.; Weinlich, J. *J. Am. Chem. Soc.*, **1966**, *88*, 4228. Dutcher, J. D.; Walters, D. R.; Wintersteiner, O. *J. Org. Chem.* **1963**, *28*, 995. Dutcher, J. D.; Young, M. B.; Sherman, J. H.; Hibbits, W. E.; Walters, D. R. *Antibiot. Ann.* **1957**, 866. von Saltza, M.; Dutcher, J. D.; Reid, J.; Wintersteiner, O. *J. Org. Chem.* **1963**, *28*, 999. (c) X-ray analysis: Ganis, P.; Avitabile, G.; Mechlinski, W.; Schaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560. Mechlinski, W. Schaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873.

from the "chiral pool"[7] constitutes another approach to the solution of this problem. For instance, a synthesis of **21**, the common precursor for both **22** and **23** can be achieved from D-glucose through a sequence of 10 steps, including three known steps for conversion of D-glucose to **24**;[8] (i) removal of one acetonide protecting group,[9] (ii) conversion of the liberated diol to its thiocarbonate, (iii) olefin formation via desulfurization,[10] (iv) introduction of a terminal hydroxyl group via hydroboration and oxidation,[11] (v) benzylation, (vi) removal of the acetonide, and (vii) sodium borohydride reduction (see Scheme I). Compound **21** is converted in a standard fashion to compound **22**, which has been found to be identical with compound **22a**, derived from **16**, except for signs of rotation. Successive treatments of **21** with sodium metaperiodate and sodium borohydride yield **23**, which in turn is converted to **25**. Compound **25** has also been derived from **19**, thus establishing the absolute configuration of **19**.

In evaluating the two approaches, the reductive epoxide ring opening and sugar routes, the former appears to be applicable to a wider range of target molecules than the latter, and to be more efficient in terms of the number of steps involved. The reductive epoxide ring opening route is also more flexible for the purpose of designing a scheme to synthesize a complex molecule. This work and the preceding paper[1] outlines our approach to the synthesis of both the 1,2- and 1,3-diol systems. The structure of the C(1)–C(19) fragment of amphotericin B (**20**) is indeed tailor-made for the application of the newly developed methodologies, and synthetic work toward this target molecule is in progress.

Acknowledgment. We are grateful to the National Science Foundation, Eli Lilly (unrestricted grant to K. B.S.), and Hoffmann-La Roche (unrestricted grant to S.M.) for generous financial support. P.M. and S.M.V. are a National Cancer Institute Trainee (NCI Grant 2-T32-CA-09112-02) and a National Science Foundation Fellowship holder, respectively. V.S.M. thanks the Fundacion Juan March of Spain for a Fellowship. High-resolution mass spectra were provided by the facility supported by the National Institutes of Health (Grant RR 00317, principal investigator, Professor K. Biemann, from the Biotechnology Resources Branch, Division of Research Resources).

Supplementary Material Available: A listing of spectral data and specific optical rotations for all new compounds prepared in this work (4 pages). Ordering information is given on any current masthead page.

(7) For recent reviews, see (a) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159. (b) Fraser-Reid, B. *Ibid.* **1975**, *8*, 192. (c) Seebach, D.; Hungerbühler, E. "Modern Synthetic Methods 1980"; Scheffold, R., Ed.; Salle and Sauerländer-Verlag: Frankfurt and Aarau, 1980.

(8) (a) Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.* **1981**, *53*, 15. (b) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718. (c) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.

(9) Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, *2*, 318.

(10) Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677.

(11) Direct conversion of the thiocarbonate to the primary alcohol via deoxygenation of the secondary alcohol reported by Barton and Subramanian (ref 7b) provided, in our hands, a mixture of the primary and secondary alcohols in a ratio of 3:1.

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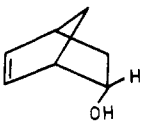
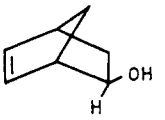
Retro-Diels–Alder Cleavage of *endo*-Bicyclo[2.2.1]hepta-5-en-2-ol

Summary: *endo*-Bicyclo[2.2.1]hepta-5-en-2-ol (**1a**) on reaction with phenylmagnesium bromide was found to yield 1-phenylethanol, arising from a retro-Diels–Alder cleavage into cyclopentadiene and acetaldehyde.

Sir: There are several reports in the literature demonstrating the additions of Grignard reagents to isolated olefins, which also have hydroxyl groups at suitable positions.[1] Thus, the title compound, **1a**, was shown to undergo allylation by the action of allylmagnesium bromide.[1e,g] In the present paper we report a fragmentation reaction of **1a** when phenylmagnesium bromide was used. Such a fragmentation has not been reported by earlier workers in studies with allylmagnesium bromide.



1a



1b

Compound **1a** was refluxed with 2 equiv of phenylmagnesium bromide in ether for 24 h. After the workup, no product corresponding to the phenylation of the double bond was detected. However, 1-phenylethanol (40–50%, based on **1a**) and cyclopentadiene dimer (5%) along with about 50% of unreacted starting material were detected by gas chromatography. The products were isolated by preparative gas chromatography and characterized by IR, NMR, and mass spectra. It was also confirmed that **1a** had not undergone isomerization to the exo isomer **1b** during the reaction. It was suspected that the starting material underwent a retro-Diels–Alder reaction as represented in Scheme I and that the acetaldehyde reacted with excess phenylmagnesium bromide to yield the observed product.

The cleavage of **1a** could be affected also under non-Grignard conditions. Thus, after **1a** was refluxed in ether for 24 h with anhydrous magnesium bromide (1:1 molar ratio) or when the sodium salt of **1a** obtained by the addition of 1 equiv of sodium hydride was refluxed for 24 h in the same solvent, only about 50% of the starting material could be recovered (quantitative analysis by gas chromatography and by NMR spectroscopy with added diphenyl ether as an internal standard). By connecting the top of the reflux condenser to a liquid nitrogen trap, cyclopentadiene (identified as the maleic anhydride adduct) and acetaldehyde (identified as the 2,4-dinitrophenylhydrazone) could be isolated. When **1a** was refluxed with 1 equiv of benzaldehyde and anhydrous magnesium bromide (in the presence of a trace of sodium hydroxide), cinnamaldehyde could be isolated, testifying to the formation of acetaldehyde anion during the reaction. It was further shown that under the reaction conditions the exo isomer, **1b**, was left unaffected.

The reaction is formally similar to a Grob fragmentation, except that the preferred reaction of the endo alcohol

(1) (a) Eisch, J. J.; Husk, G. R. *J. Am. Chem. Soc.* **1965**, *87*, 4194. (b) Cherest, M.; Felkin, H.; Frajerman, C.; Lion, C.; Roussi, G.; Swierczewski, G. *Tetrahedron Lett.* **1966**, 875. (c) Felkin, H.; Kaeseberg, C. *Ibid.* **1970**, 4587. (d) Eisch, J. J.; Merkley, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1148. (e) Richey, H. G., Jr.; Wilkins, C. W., Jr.; Brown, B. S.; Moore, R. E. *Tetrahedron Lett.* **1976**, 723. (f) Eisch, J. J.; Merkley, J. H.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 587. (g) Richey, H. G., Jr.; Wilkins, C. W., Jr. *Ibid.* **1980**, *45*, 5027.

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